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REMARKS

Claims 19-41 and 43-46 were pending prior to this response. By the present communication, no claims are added or cancelled and claims 19 and 41 have been amended to define Applicants' invention with greater particularity. The amendments add no new matter, the claim amendments being fully supported by the specification and original claims. Accordingly, claims 19-41, and 43-46 are currently pending.

The Rejection under 35 U.S.C. § 112, First Paragraph

Applicants respectfully traverse the rejection of claims 19-41 and 43-46 as failing to comply with the written description requirement under 35 U.S.C. § 112, first paragraph, for allegedly introducing new matter.

Despite Applicants' showing of support for the amendments to claims 19 and 41, the Examiner asserts:

> . . . the DNA as recited in claim 19 is not limited to prokaryotic DNA or to genomic DNA . . . there is no requirement that "prokaryotic genomic DNA be "naturally occurring" as such DNA may be obtained, e.g., from a bacterial strain whose genomic DNA sequences have been altered by a mutagen, e.g., UV radiation. As such, one would clearly recognize that the term "prokaryotic genomic DNA" does not provide support for the term "naturally occurring" (Office Action, page 4).

Applicants respectfully disagree with the logic of the Examiner's assertions that serve as the basis for maintaining the rejection. First, the plain dictionary meaning of the phrase "naturally occurring" is "as found in nature". This is, indeed, the meaning of the term as used throughout the Specification. Moreover, Applicants disagree with the Examiner's assertion that DNA that has been altered in nature by exposure to UV is somehow not "naturally occurring." However, Applicants submit that, in the unlikely event DNA existing in the genome of an organism has been altered by a mutagen while in the natural setting, the recovered DNA is still "genomic DNA" for that organism and "naturally occurring" (i.e., unaltered by the hand of man). Moreover, it is submitted that the passage from page 22 of the Specification recited above renders it clear that Applicants described "naturally occurring" DNA as coming from either

prokaryotic or eukaryotic organisms. Thus, it is the position of the Applicants that the newly added claim limitations are supported in the specification "through express, implicit, or inherent disclosure" in compliance with the requirements of MPEP 2163.

Claims 19-41 have been rejected as failing to comply with the written description requirement. The Action states that claim 19 has been amended to recite the limitation "wherein each clone contains DNA from a single organism," which allegedly is not supported in the original disclosure (MPEP 714.02 and 2163.06). Applicants respectfully disagree with this assertion because the specification as originally filed describes clones containing DNA from a single organism. Support for this amended language may be found in the specification at page 23, second paragraph; page 24, second paragraph; page 25, lined 9-13; and page 36, third paragraph. Therefore, Applicants submit that the recitation has support in the specification in compliance with MPEP 714.02 and 2163.06.

Accordingly, it is submitted that Applicants' amendments add no new matter to claims 19 and 41 and reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

The Rejection under 35 U.S.C. § 102(b)

Applicants respectfully traverse the rejection of claims 19, 20, 22, 24-29, 35, 37-39 and 43-45 under 35 U.S.C. § 102(b) as allegedly being anticipated by Thompson et al. (U.S. Patent 5,824,485; hereinafter "Thompson") as originally applied in the Office Action mailed herein December 07, 1999 and maintained in subsequent Office Actions. Applicants submit that the invention methods for identifying a bioactivity or biomolecule of interest using high throughput screening of DNA, as defined by amended claim 19, distinguish over Thompson at least by requiring:

> a) normalizing the representation of organisms present in a sample containing naturally occurring DNA from more than one organism to increase representation of rare species; and b) contacting a bioactive substrate that is fluorescent in the presence of the bioactivity or biomolecule of interest with a library containing a plurality of clones

containing normalized DNA prepared in (a, wherein each clone contains DNA from a single organism; . . .

In the Specification, Applicants describe the effect of "normalizing" DNA in a sample as follows:

> The present invention can further optimize methods for isolation of activities of interest from a variety of sources, including consortias of microorganisms, primary enrichments, and environmental "uncultivated" samples, to make libraries which have been "normalized" in their representation of the genome populations in the original samples. and to screen these libraries for enzyme and other bioactivities. Libraries with equivalent representation of genomes from microbes that can differ vastly in abundance in natural populations are generated and screened. This "normalization" approach reduces the redundancy of clones from abundant species and increases the representation of clones from rare species. (Specification, page 24, lines 11-22).

Thus, the invention methods require preparation of a library in which representation of the various species from the original sample has been adjusted to equalize representation of organisms in the library.

Thompson is silent regarding "normalizing" DNA obtained from a mixture of species to allow more equal representation in a library of the DNA from the organisms present in the original sample. Thompson's disclosure of utilizing uncultured organisms in the sample to avoid dilution of slow growing members in a mixed population (Thompson, Col. 14, lines 46-54) and repairing damaged DNA to avoid loss of species from the sample (Thompson, Col. 17, lines 33-40) is to be distinguished from Applicants' requirement of "normalizing" the representation of species in the sample.

Applicants submit that Thompson does not change the abundance of species present in the sample. Thompson's techniques would not result in equal representation of the organisms in the sample because Thompson does not disclose that only rare DNA would be need to be repaired or would be slow growing. For example, over-represented species are just as likely to have damaged DNA as underrepresented species unless it is predetermined that the DNA being repaired is from a rare species. In short, Thompson fails to disclose any procedure by which the

complexity of the DNA population isolated is analyzed and treated in such a way that equalization in copy numbers of clones in the mixed population is attained.

In addition, as previously presented in the Response to the Office Action dated October 9, 2003, Applicants disagree with the Examiner's position that the following passage from Thompson illustrates that Thompson's disclosure meets the requirements of Applicants' methods for identifying a "naturally occurring" bioactivity or biomolecule, as defined by amended claim 19, especially the requirement in claim 19 that "each clone contains DNA from a single one of the organisms." The passage from Thompson quoted by the Examiner as illustrating that Thompson screens "naturally occurring" DNA states:

> . . ."[t]the naturally-occurring pathways of the donor organisms may thus be reconstituted in the host organism" such that "[t]he metabolic pathways of the donor organism may also interact with metabolic pathways resident in the host organism to generate novel compounds or compounds not normally produced by the host organism" (column 5, top)." (Office Action, page 8).

Applicants disagree that this passage from Thompson illustrates the term "naturally occurring" as used in Applicants specification and claims. As rationale for maintaining the rejection, the Examiner asserts that Exhibits A, B and C referred to in the previous response were not attached to the response. As Exhibits A, B and C support Applicant's position that Thompson here describes a species of "combinatorial library" wherein DNA native to the host combines with DNA obtained from the donor organism, Applicants provide the allegedly missing documents as Exhibits A, B and C to this response. The Examiner's consideration of these documents in the light of the arguments in the previous response is respectfully requested.

Moreover, in view of Thompson's failure to disclose normalization of the species to increase representation of rare species included in the library prior to screening or use of "naturally occurring" DNA in the library to be screened, Applicants submit that Thompson fails to disclose each and every element of claims 19, 20, 22, 24-29, 35, 37-39 and 43-45 as would be required to establish anticipation under 35 U.S.C. § 102 (e).

The Rejection under 35 U.S.C. § 103

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

A. Applicants respectfully traverse the rejection of claim 23 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above).

The deficiencies of Thompson described above for disclosing the invention methods of claim 19 apply equally and are incorporated here with regard to claim 23, which depends from claim 19. In addition, Applicants respectfully submit that Thompson fails to suggest the invention methods and would not motivate those of skill in the art to modify Thompson to arrive at the presently presented invention methods because the thrust of Thompson's disclosure is devoted to preparation and screening of libraries in which the representation of clones has not been normalized and/or combinatorial gene libraries.

Specifically, Thompson's disclosure of utilizing uncultured organisms to make sure that the representation of organisms in the library is not skewed from that in the original sample and using "reconstituted metabolic pathways" does not suggest and would not motivate those of skill in the art to "normalize" the representation of organisms in the library to avoid overrepresentation of certain clones or to look to the DNA of a single donor organism for detection of a "naturally occurring" biomolecule or bioactivity of interest, as the term "naturally occurring" is used in Applicants' specification and claims. Thus, Applicants submit that

Thompson's disclosure does not establish *prima facie* obviousness of the invention method of claim 23 under 35 U.S.C. § 103.

B. Applicants respectfully traverse the rejection of claims 30-32 and 34 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above) and Miao et al, Biotechnology and Bioengineering (1993) 42:708-715, hereinafter "Miao".

Applicants' remarks above regarding the failure of Thompson to render obvious claim 19 and 23 apply equally and are incorporated here. In addition, Applicants submit that the disclosure of Miao fails to remedy the deficiencies of Thompson under 35 U.S.C. § 103 with regard to claim 19, from which claims 30-32 and 34 depend. Miao's disclosure pertains to use of C_{12}FDG as a fluorescent substrate in FACS screening of single bacterial cells of one species (i.e., E. coli). Thus, like Thompson, Miao is completely silent regarding screening of a library containing a plurality of clones, wherein each clone contains DNA from a single one of the donor organisms.

Indeed, Miao's disclosure does not pertain to screening of a plurality of species, Applicants submit that the combined disclosures of Thompson and Miao would be insufficient to motivate those of skill in the art to create a method for "normalizing" the representation of organisms prior to creating the library to avoid overrepresentation of certain clones or to look to the DNA of a single donor organism for detection of a "naturally occurring" biomolecule or bioactivity of interest, as the term "naturally occurring" is used in Applicants' specification and claims for any purpose, let alone for an activity produced in a clone that triggers fluorescence in a bioactive substrate.

In addition, even if those of skill in the art were motivated by the combined disclosures of Thompson and Miao to arrive at the invention methods, Applicants submit that the cited art would fail to provide the reasonable expectation of success that is required to show unpatentability under 35 U.S.C. § 103. Neither Thompson nor Miao discusses any technique by which the DNA from the organisms of a sample is normalized to increase representation of the rarer species present in the sample prior to making a library or by which fluorescence screening can be adapted to discover a bioactivity or a biomolecule encoded by DNA from a single donor organism among a plurality of such organisms. Therefore, those of skill in the art would not be

justified in assuming success in the outcome of any technique that might be devised by modification of the combined disclosures of Thompson and Miao.

Accordingly, Applicants respectfully submit that the combined disclosures of Thompson and Miao, including Miao's disclosure regarding rapid screening using C_{12}FDG, are not sufficient to teach or suggest Applicants' invention of dependent claims 30-32 and 34, which contain the requirements of amended claim 19. Thus, Applicants respectfully submit that claims 30-32 and 34 are not *prima facie* obvious over Thompson, or the combined disclosures of Thompson and Miao.

C. Applicants respectfully traverse the rejection of claim 33 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above) and Miao (as above) and further in view of Hirata et al. (U.S. Patent No. 4,861,718; hereinafter "Hirata").

Applicants submit that the remarks above regarding the failure of the combined disclosures of Thompson and Miao to render obvious the invention of claims 19 (and 30-32 and 34) under 35 U.S.C. § 103 apply equally and are incorporated here. The Examiner acknowledges that the combination of Thompson and Miao is not sufficient to block patentability of claim 33 under 35 U.S.C. § 103 (Office Action of October 9, 2003, page 13, bottom paragraph).

In addition, Applicants submit that the disclosure of Hirata fails to remedy the deficiencies of Thompson-Miao disclosure with respect to claim 19. Hirata's disclosure is relied upon by the Examiner as disclosing the heating of a nucleic acid encoding a thermostable beta-galactosidase having a temperature optimum at 70 degrees Celcius. However, like Thompson and Miao, Hirata is completely silent regarding screening of a library containing a plurality of clones, wherein each clone contains DNA from a single one of the donor organisms.

Indeed, since Hirata's disclosure does not pertain normalization of the representation of a plurality of clones in a library or to high throughput screening of a library of a plurality of organisms, with each clone containing DNA from only one of the organisms, to determine fluorescence, as is required in amended claim 19, Applicants submit that the combined disclosures of Thompson and Miao and Hirata would be insufficient to motivate those of skill in the art to modify the combined disclosures to arrive at such a method at any temperature.

In addition, even if those of skill in the art were motivated by the combined Thompson-Miao-Hirata disclosures to arrive at the invention methods, Applicants submit that the cited art would fail to provide the reasonable expectation of success that is required to show unpatentability under 35 U.S.C. § 103. Because none of the three references discusses any technique by which the DNA of organisms in a screening library can be normalized to increase their representation or by which fluorescence screening can be adapted to discover a bioactivity or a biomolecule encoded by DNA from a single donor organism among a plurality of such organisms, those of skill in the art would not be justified in assuming success in the outcome of any technique that might be devised by modification of the combined Thompson-Miao-Hirata disclosures. Thus, Applicants respectfully submit that claim 33 is not *prima facie* obvious over the cited art.

D. Applicants respectfully traverse the rejection of claims 21, 36, 40 and 46 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above) in view of Minshull et al. (U.S. Patent No. 5,837,458; hereinafter "Minshull").

The remarks above regarding the failure of Thompson to render obvious under 35 U.S.C. § 103 the invention of claims 19 and 20, from which claims 21, 26, 40 and 46 depend, apply equally and are incorporated here. In addition, Applicants submit that the disclosure of Minshull fails to remedy the deficiencies of Thompson acknowledged by the Examiner with regard to the claims at issue (Office Action of October 9, 2003, page 15, second paragraph).

Minshull is relied upon for allegedly disclosing cellular and metabolic engineering by recursive sequence recombination. However, Applicants submit that the combined disclosures of Minshull and Thompson fail to disclose or suggest the invention methods for identifying a bioactivity or biomolecule of interest using high throughput screening of DNA, as defined by amended claim 19, due to failure of either reference to suggest procedures for normalizing the representation of organisms in the library or for screening a DNA library containing clones of a plurality of organisms wherein each clone contains DNA of a single one of the organisms to detect those clones containing naturally occurring DNA from one of the organisms that is sufficient to cause the bioactive substrate to fluoresce.

In addition, Applicants submit that even if those of skill in the art were motivated by the combined disclosures of Thompson and Minshull to arrive at the invention methods, the combination of Thompson and Minshull would fail to provide the reasonable expectation of success that is required to show unpatentability under 35 U.S.C. § 103. As neither Thompson nor Minshull discusses any technique for normalizing the representation of organisms in the library or by which fluorescence screening can be adapted to discover a bioactivity or a biomolecule encoded by DNA from a single donor organism among a plurality of such organisms, Applicants submit those of skill in the art would not be justified in assuming success in the outcome of any technique that might be devised by modification of the combined disclosures of Thompson and Minshull to arrive at such results. Accordingly, Applicants submit that *prima facie* obviousness of claim 33 is not established over the combined disclosures of Thompson and Minshull.

E. Applicants respectfully traverse the rejection of claim 41 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above) in view of Minshull (as above) and further in view of Loveland et al. (*Appl Environ Microbiol* 60:12-18; hereinafter "Loveland").

The remarks above regarding the failure of the combined disclosures of Thompson and Minshull to render obvious under 35 U.S.C. § 103 the invention of claims 19 and 40, from which claim 41 depends, apply equally and are incorporated here.

In addition, Applicants submit that the disclosure of Loveland fails to remedy the deficiencies of Thompson acknowledged by the Examiner with regard to the claims at issue (Office Action of October 9, 2003, page 15, second paragraph). Loveland is relied upon for allegedly disclosing "isolation of a polynucleotide encoding a beta-galactosidase from a psychrotropic bacterium that exhibited a temperature optimum about 20 degrees Celsius below that of Escherichia coli beta-galactosidase" (Office Action, page 14). However, Loveland's disclosure pertains to isolation of an organism using techniques of amino acid analysis, enzyme test strips, and cell growth assays using ONPG as the substrate for testing for enzyme activity. At no point does Loveland disclose or suggest "isolation of a polynucleotide encoding [the enzyme]" as asserted by the Examiner.

Moreover, Applicants submit that the combined disclosures of Minshull and Thompson fail to disclose or suggest the invention methods for identifying a bioactivity or biomolecule of interest using high throughput screening of DNA, as defined by amended claim 19, due to failure of any one of the references to suggest procedures for normalizing the representation of DNA of organisms in the library or for screening a library containing clones of a plurality of organisms wherein each clone contains "naturally occurring" donor DNA of a single one of the organisms to detect a clones from one of the organisms that is sufficient to cause the bioactive substrate to fluoresce.

In addition, Applicants submit that even if those of skill in the art were motivated by the combined disclosures of Thompson, Minshull and Loveland to arrive at the invention methods, the combination of Thompson, Minshull and Loveland would fail to provide the reasonable expectation of success that is required to show unpatentability under 35 U.S.C. § 103. As not one of Thompson, Minshull and Loveland discusses any technique for normalizing the representation of DNA of multiple organisms in the library or for adapting fluorescence screening to discover a bioactivity or a biomolecule encoded by DNA from a single donor organism among a plurality of such organisms, Applicants submit those of skill in the art would not be justified in assuming success in the outcome of any technique that might be devised by modification of the combined disclosures of Thompson Minshull and Loveland to arrive at such results. Accordingly, Applicants submit that *prima facie* obviousness of claim 41 is not established over the combined disclosures of Thompson, Minshull and Loveland.

In view of the above amendments and remarks, reconsideration and withdrawal of the various rejections under 35 U.S.C. § 103 are respectfully requested.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that the pending claims clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: July 16, 2004

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Attachments: Exhibits A, B and C for Response mailed February 6, 2004

Neugenesis
A Biotechnology Company

COMBINATORIAL BIOLOGY TECHNOLOGY

Neugenesis' combinatorial biology technology (the CombiKARYON™ system) mimics the immune system's ability to generate diversity in antibodies, and expands the application to all heteromeric proteins. The company uses this technology to discover and improve complex proteins. It is an efficient and cost-effective method to improve a protein's stability, affinity, receptor binding capacity, and therapeutic efficacy, thereby enhancing the value of the protein, and decreasing the risk of clinical failure.

Using Combinatorial Biology to Generate Diversity

An outgrowth of Neugenesis' protein production systems, CombiKARYON™ uses the unique features of the filamentous fungus, *Neurospora crassa*, to create combinatorial panels of heavy and light chains of a heteromeric protein and to build libraries of diverse, new, fully assembled proteins. Variants of each subunit gene are generated within the host by Neugenesis' proprietary technology. Strains carrying these new gene sequences are fused to one another in all possible combinations to produce libraries in the following manner.

VARIANT	Light chain 1	Light chain 2	Light chain 3	Light chain 4
Heavy chain 1	L1H1	L2H1	L3H1	L4H1
Heavy chain 2	L1H2	L2H2	L3H2	L4H2
Heavy chain 3	L1H3	L2H3	L3H3	L4H3
Heavy chain 4	L1H4	L2H4	L3H4	L4H4

In this illustration, 16 unique monoclonal antibody combinations are produced from 4 light and 4 heavy chain subunit variants. In a standard microtiter plate configuration, 96 unique combinations would be produced when 12 variants of one subunit are arrayed against 8 variants of the second subunit. With CombiKARYON™, this would be done with 20 total transformations. Traditional protein engineering techniques would require 96 transformations after a complicated reassembly process of the subunit genes. These burdensome steps are eliminated using Neugenesis' combinatorial biology approach. The advantages become more apparent in larger libraries. For example, a 100x100

matrix to create 10,000 combinations would require 200 transformations in the CombiKARYON™ system, and 10,000 transformations using traditional techniques. This technology can also be used to create combinations of more than two subunits, to geometrically increase the diversity. The last step is to screen the combinatorial libraries for new proteins with the desired characteristics.

Applying Combinatorial Biology to Drug Discovery and Improvement

CombiKARYON™ is an expedient approach for companies involved in developing difficult and complex protein therapeutics. The applications of the technology are numerous. For example, Neugenesis' technology may be applied to protein hits to improve the characteristics such as binding capacity or stability. By designing and creating small changes in the original molecule, Neugenesis is able to fine-tune the protein without dramatically changing the protein's core structure, which has already been selected for through years of evolution. This technology can also be applied to protein drug candidates already in pre-clinical and clinical trials. The failure rate of drug candidates in the development process is estimated to be at least 60-80%. Neugenesis' combinatorial biology system may help by providing a means to more efficiently fine-tune these candidates into better, therapeutically useful molecules.

Other potential applications of CombiKARYON™ include drug combination research and hybridization. In drug combination research, combinatorial biology enables rapid and inexpensive creation of any number of combinations of synergistic proteins, which can then be screened for the most effective combination. In hybridization, combinatorial biology can be used to develop hybrid molecules with both binding and effector moieties, improving the specificity of therapeutic agents.

In addition, cultures of desirable molecules identified through this technology can be easily expanded to produce large-scale quantities of the new heteromeric protein for further evaluation, since the protein is already in a *Neurospora* production strain.

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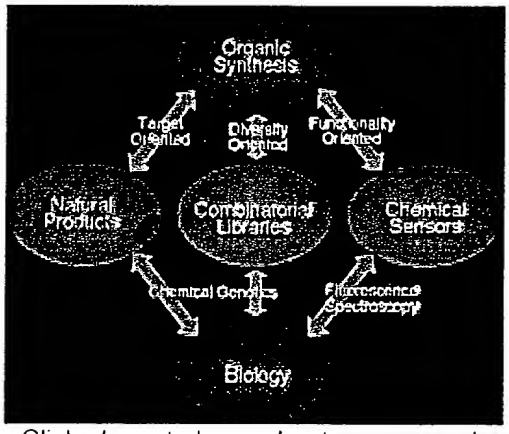

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Glossary of Terms Used in Medicinal Chemistry
(IUPAC Recommendations 1998)

A to H

Contents

Active transport*

Active transport is the carriage of a solute across a biological membrane from low to high concentration that requires the expenditure of (metabolic) energy.

Address-message concept

Address-message concept refers to compounds in which part of the molecule is required for binding (address) and part for the biological action (message).

ADME

Abbreviation for **Absorption, Distribution, Metabolism, Excretion**. (See also **Pharmacokinetics**; **Drug disposition**).

Affinity

Affinity is the tendency of a mc ule to associate with another. The **affi y** of a **drug** is its ability to bind to its biological target (**receptor**, **enzyme**, transport system, etc.) For pharmacological **receptors** it can be thought of as the frequency with which the **drug**, when brought into the proximity of a **receptor** by diffusion, will reside at a position of minimum free energy within the force field of that **receptor**.

For an **agonist** (or for an **antagonist**) the numerical representation of **affinity** is the reciprocal of the equilibrium dissociation constant of the ligand-**receptor** complex denoted K_A, calculated as the rate constant for offset (k_{-1}) divided by the rate constant for onset (k_1).

Agonist***

An **agonist** is an endogenous substance or a **drug** that can interact with a **receptor** and initiate a physiological or a pharmacological response characteristic of that **receptor** (contraction, relaxation, secretion, **enzyme** activation, etc.).

Allosteric binding sites

Allosteric binding sites are contained in many **enzymes** and **receptors**. As a consequence of the binding to **Allosteric binding sites**, the interaction with the normal ligand may be either enhanced or reduced.

Allosteric enzyme*

An **allosteric enzyme** is an **enzyme** that contains a region to which small, regulatory molecules ("effectors") may bind in addition to and separate from the substrate binding site and thereby affect the catalytic activity.

On binding the effector, the catalytic activity of the **enzyme** towards the substrate may be enhanced, in which case the effector is an activator, or reduced, in which case it is a de-activator or inhibitor.

Allosteric regulation

Allosteric regulation is the regulation of the activity of **allosteric enzymes**. (See also **Allosteric binding sites**; **Allosteric enzymes**).

Analog

An **analog** is a **drug** whose structure is related to that of another **drug** but whose chemical and biological properties may be quite different. (See also **Congener**).

Antagonist***

An **antagonist** is a **drug** or a compound that opposes the physiological effects of another. At the **receptor** level, it is a chemical entity that opposes the **receptor**-associated responses normally induced by another bioactive agent.

Antimetabolite***

An **antimetabolite** is a structural **analog** of an intermediate (substrate or **coenzyme**) in a physiologically

occurring metabolic pathway th cts by replacing the natural substrate ; blocking or diverting the biosynthesis of physiologically important substances.

Antisense molecule

An **antisense molecule** is an **oligonucleotide** or **analog** thereof that is complementary to a segment of RNA (ribonucleic acid) or DNA (deoxyribonucleic acid) and that binds to it and inhibits its normal function.

Autacoid

An **autacoid** is a biological substance secreted by various cells whose physiological activity is restricted to the vicinity of its release; it is often referred to as local **hormone**.

Autoreceptor

An **autoreceptor**, present at a nerve ending, is a **receptor** that regulates, via positive or negative feedback processes, the synthesis and/or release of its own physiological ligand. (See also **Heteroreceptor**).

Bioassay***

A **bioassay** is a procedure for determining the concentration, purity, and/or biological activity of a substance (e.g., vitamin, **hormone**, plant growth factor, antibiotic, **enzyme**) by measuring its effect on an organism, tissue, cell, **enzyme** or **receptor** preparation compared to a standard preparation.

Bioisostere

A **bioisostere** is a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based. (See also **Isostere**)

Bioprecursor prodrug

A **bioprecursor prodrug** is a **prodrug** that does not imply the linkage to a carrier group, but results from a molecular modification of the active principle itself. This modification generates a new compound, able to be transformed metabolically or chemically, the resulting compound being the active principle.

Biotransformation

Biotransformation is the chemical conversion of substances by living organisms or **enzyme** preparations.

CADD

See **Computer-assisted drug design**.

Carrier-linked prodrug (Carrier prodrug)

A **carrier-linked prodrug** is a **prodrug** that contains a temporary linkage of a given active substance with a transient carrier group that produces improved physicochemical or pharmacokinetic properties and that can be easily removed *in vivo*, usually by a hydrolytic cleavage.

Cascade prodrug

A **cascade prodrug** is a **prodrug** for which the cleavage of the carrier group becomes effective only after unmasking an activating group.

Catabolism***

Catabolism consists of reactions involving endogenous organic substrates to provide chemically available energy (e.g., ATP) and/or to generate metabolic intermediates used in subsequent anabolic reactions.

Catabolite

A **catabolite** is a naturally occurring **metabolite**.

Clone*

A **clone** is a population of genetically identical cells produced from a common ancestor. Sometimes, "**clone**" is also used for a number of recombinant DNA (deoxyribonucleic acid) molecules all carrying the same inserted sequence.

Codon*

A **codon** is the sequence of three consecutive **nucleotides** that occurs in mRNA which directs the incorporation of a specific amino acid into a protein or represents the starting or termination signals of protein synthesis.

Coenzyme

A **coenzyme** is a dissociable, low-molecular weight, non-proteinaceous organic compound (often **nucleotide**) participating in enzymatic reactions as acceptor or donor of chemical groups or electrons.

Combinatorial synthesis

Combinatorial synthesis is a process to prepare large sets of organic compounds by combining sets of building blocks.

Combinatorial library

A **combinatorial library** is a set of compounds prepared by **combinatorial synthesis**.

CoMFA

See **Comparative Molecular Field Analysis**.

Comparative Molecular Field Analysis (CoMFA)**

Comparative molecular field a ysis (CoMFA) is a **3D-QSAR** metho at uses statistical correlation techniques for the analysis of the quantitative relationship between the biological activity of a set of compounds with a specified alignment, and their three-dimensional electronic and steric properties. Other properties such as hydrophobicity and hydrogen bonding can also be incorporated into the analysis. (See also **Three-dimensional Quantitative Structure-Activity Relationship [3D-QSAR]**).

Computational chemistry**

Computational chemistry is a discipline using mathematical methods for the calculation of molecular properties or for the simulation of molecular behaviour.

Computer-assisted drug design (CADD)**

Computer-assisted drug design involves all computer-assisted techniques used to discover, design and optimize biologically active compounds with a putative use as **drugs**.

Congener***

A **congener** is a substance literally *con-* (with) *generated* or synthesized by essentially the same synthetic chemical reactions and the same procedures. **Analogs** are substances that are analogous in some respect to the prototype agent in chemical structure.

Clearly **congeners** may be **analogs** or vice versa but not necessarily. The term **congener**, while most often a synonym for homologue, has become somewhat more diffuse in meaning so that the terms **congener** and **analog** are frequently used interchangeably in the literature.

Cooperativity

Cooperativity is the interaction process by which binding of a ligand to one site on a macromolecule (**enzyme**, **receptor**, etc.) influences binding at a second site, e.g. between the substrate binding sites of an **allosteric enzyme**. Cooperative **enzymes** typically display a sigmoid (S-shaped) plot of the reaction rate against substrate concentration. (See also **Allosteric binding sites**).

3D-QSAR

See **Three-dimensional Quantitative Structure-Activity Relationship**.

De novo* design*

***De novo* design** is the design of bioactive compounds by incremental construction of a ligand model within a model of the **receptor** or **enzyme** active site, the structure of which is known from X-ray or nuclear magnetic resonance (NMR) data.

Disposition

See **Drug disposition**.

Distomer

A **distomer** is the enantiomer o. chiral compound that is the less poten . a particular action. This definition does not excude the possibility of other effect or side effect of the **distomer** (See also **Eutomer**).

Docking studies

Docking studies are molecular modeling studies aiming at finding a proper fit between a ligand and its binding site.

Double-blind study

A ***double-blind study*** is a clinical study of potential and marketed **drugs**, where neither the investigators nor the subjects know which subjects will be treated with the active principle and which ones will receive a placebo.

Double prodrug (or pro-prodrug)

A **double prodrug** is a biologically inactive molecule which is transformed *in vivo* in two steps (enzymatically and/or chemically) to the active species.

Drug***

A **drug** is any substance presented for treating, curing or preventing disease in human beings or in animals. A **drug** may also be used for making a medical diagnosis or for restoring, correcting, or modifying physiological functions (e.g., the contraceptive pill).

Drug disposition

Drug disposition refers to all processes involved in the absorption, distribution **metabolism** and excretion of **drugs** in a living organism.

Drug latentiation

Drug latentiation is the chemical modification of a biologically active compound to form a new compound, which *in vivo* will liberate the parent compound. **Drug latentiation** is synonymous with **prodrug** design.

Drug targeting

Drug targeting is a strategy aiming at the delivery of a compound to a particular tissue of the body.

Dual action drug

A **dual action drug** is a compound which combines two desired different pharmacological actions at a similarly efficacious dose.

Efficacy

Efficacy describes the relative intensity with which **agonists** vary in the response they produce even

when they occupy the same nur r of **receptors** and with the same **affi** . **Efficacy** *is not* synonymous to **Intrinsic activity**.

Efficacy is the property that enables **drugs** to produce responses. It is convenient to differentiate the properties of **drugs** into two groups, those which cause them to associate with the **receptors (affinity)** and those that produce stimulus (**Efficacy**). This term is often used to characterize the level of maximal responses induced by **agonists**. In fact, not all **agonists** of a **receptor** are capable of inducing identical levels of maximal responses. Maximal response depends on the efficiency of **receptor** coupling, i.e., from the cascade of events, which, from the binding of the **drug** to the **receptor**, leads to the observed biological effect.

Elimination

Elimination is the process achieving the reduction of of the concentration of a **xenobiotic** including its **metabolism**.

Enzyme*

An **enzyme** is a macromolecule, usually a protein, that functions as a (bio) catalyst by increasing the reaction rate.

In general, an **enzyme** catalyzes only one reaction type (reaction selectivity) and operates on only one type of substrate (substrate selectivity). Substrate molecules are transformed at the same site (regioselectivity) and only one or preferentially one of chiral a substrate or of a racemate is transformed (enantioselectivity[special form of stereoselectivity]).

Enzyme induction*

Enzyme induction is the process whereby an (inducible) **enzyme** is synthesized in response to a specific inducer molecule. The inducer molecule (often a substrate that needs the catalytic activity of the inducible **enzyme** for its **metabolism**) combines with a repressor and thereby prevents the blocking of an operator by the repressor leading to the translation of the gene for the **enzyme**.

Enzyme repression*

Enzyme repression is the mode by which the synthesis of an **enzyme** is prevented by repressor molecules.

In many cases, the end product of a synthesis chain (e.g., an amino acid) acts as a feed-back corepressor by combining with an intracellular aporepressor protein, so that this complex is able to block the function of an operator. As a result, the whole operation is prevented from being transcribed into mRNA, and the expression of all **enzymes** necessary for the synthesis of the end product **enzyme** is abolished.

Eudismic ratio

Eudismic ratio is the **potency** of the **eutomer** relative to that of the **distomer**.

Eutomer

The **Eutomer** is the enantiomer a chiral compound that is the more po for a particular action (See also **Distomer**).

Genome*

A **genome** is the complete set of chromosomal and extrachromosomal genes of an organism, a cell, an organelle or a virus; the complete DNA (deoxyribonucleic acid) component of an organism.

Hansch analysis**

Hansch analysis is the investigation of the quantitative relationship between the biological activity of a series of compounds and their physicochemical substituent or global parameters representing hydrophobic, electronic, steric and other effects using multiple regression correlation methodology.

Hapten***

A **hapten** is a low molecular weight molecule that contains an antigenic determinant but which is not itself antigenic unless combined with an antigenic carrier.

Hard drug

A **hard drug** is a nonmetabolizable compound, characterized either by high lipid solubility and accumulation in adipose tissues and organelles, or by high water solubility.

In the lay press the term "**Hard Drug**" refers to a powerful **drug** of abuse such as cocaine or heroin.

Heteroreceptor

A **heteroreceptor** is a **receptor** regulating the synthesis and/or the release of mediators other than its own ligand (See also **Autoreceptor**).

Homologue

The term **homologue** is used to describe a compound belonging to a series of compounds differing from each other by a repeating unit, such as a methylene group, a peptide residue, etc.

Hormone***

A **hormone** is a substance produced by endocrine glands, released in very low concentration into the bloodstream, and which exerts regulatory effects on specific organs or tissues distant from the site of secretion.

Hydrophilicity**

Hydrophilicity is the tendency of a molecule to be solvated by water.

Hydrophobicity**

Hydrophobicity is the association of non-polar groups or molecules in an aqueous environment which arises from the tendency of water to exclude non polar molecules. (See also **Lipophilicity**).

Continue with terms starting with I to X.

Return to home page for **Glossary** of Terms Used in Medicinal Chemistry.